Age at disease onset of inflammatory bowel disease is associated with later extraintestinal manifestations and complications

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Abstract: INTRODUCTION A small but increasing number of patients with inflammatory bowel disease are diagnosed during childhood or adolescence, and disease distribution and severity at onset vary according to the age at diagnosis. Clinical factors present at the time of diagnosis can be predictive of the disease course. AIM The aim of this study was to characterize disease behavior and the cumulative complications and extraintestinal manifestations 10 years after the diagnosis and to assess their association with age at diagnosis. PATIENTS AND METHODS Data of patients participating with the Swiss IBD cohort study registry, a disease duration of 10 years and a complete data set were analyzed. The outcome was defined as the cumulative change of disease behavior, the occurrence of extra-intestinal manifestations or complications, and the necessity for medical or surgical interventions. RESULTS A total of 481 patients with Crohn's disease (CD) and 386 patients with ulcerative colitis (UC), grouped according to disease onset before 10, 17, 40, or after 40 years of age, were analyzed. Despite differences in sex, initial disease location, and smoking habits, at 10 years after the diagnosis, no difference was found regarding disease behavior in CD or regarding progression of disease extension in UC. Similarly, no age-of-onset-dependent cumulative need for medical or surgical therapies was found. However, higher rates of anemia and lower rates of arthralgia and osteopenia were found in both pediatric-onset CD and UC, and a tendency toward higher rates of stomatitis in pediatric-onset CD, and of primary sclerosing cholangitis and ankylosing spondylitis in pediatric-onset UC. CONCLUSION After 10 years of disease evolution, age at disease onset is not anymore associated with disease behavior but only with a small difference in the occurrence of specific extraintestinal manifestations and complications.

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Introduction A small but increasing number of patients with inflammatory bowel disease are diagnosed during childhood or adolescence, and disease distribution and severity at onset vary according to the age at diagnosis. Clinical factors present at the time of diagnosis can be predictive of the disease course.

Aim The aim of this study was to characterize disease behavior and the cumulative complications and extraintestinal manifestations 10 years after the diagnosis and to assess their association with age at diagnosis.

Patients and methods Data of patients participating with the Swiss IBD cohort study registry, a disease duration of 10 years and a complete data set were analyzed. The outcome was defined as the cumulative change of disease behavior, the occurrence of extra-intestinal manifestations or complications, and the necessity for medical or surgical interventions.

Results A total of 481 patients with Crohn's disease (CD) and 386 patients with ulcerative colitis (UC), grouped according to disease onset before 10, 17, 40, or after 40 years of age, were analyzed. Despite differences in sex, initial disease location, and smoking habits, at 10 years after the diagnosis, no difference was found regarding disease behavior in CD or regarding progression of disease extension in UC. Similarly, no age-of-onset-dependent cumulative need for medical or surgical therapies was found. However, higher rates of anemia and lower rates of arthralgia and osteopenia were found in both pediatric-onset CD and UC, and a tendency toward higher rates of stomatitis in pediatric-onset CD, and of primary sclerosing cholangitis and ankylosing spondylitis in pediatric-onset UC.

Conclusion After 10 years of disease evolution, age at disease onset is not anymore associated with disease behavior but only with a small difference in the occurrence of specific extraintestinal manifestations and complications. Eur J Gastroenterol Hepatol 30:598–607

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC) and indeterminate colitis [IBD-unclassified (IBD-U)], is a group of chronic inflammatory conditions affecting the gastrointestinal (GI) tract. Intestinal manifestations, such as diarrhea, abdominal pain, and bleeding, are the main symptoms, but extraintestinal manifestations (EIMs) such as arthralgia, or ocular, cutaneous, or hepatic disease also reveal active inflammation. Furthermore, disease behaviour, including disease expansion, and penetrating or stenosing behavior is difficult to predict.

An increasing number of patients with IBD are diagnosed during childhood and adolescence [1–4], even though this number still represents a small percentage of all patients with IBD. In contrast to adult disease onset, there is a striking variety of pediatric-onset IBD characteristics regarding disease distribution and severity at onset, endoscopic appearance, histology, genetic background, comorbidities, complications during follow-up, and response to or choice of various treatment options [5]. It even has been speculated that pediatric-onset CD is a distinct disease entity, with probably different disease subtypes [6].

In an effort to identify predicting factors for disease evolution, numerous clinical follow-up studies have been undertaken, and a North-South disease management gradient across Europe [7], a change of disease location and increase in EIMs over the years [8], and a controversial dependency of disease evolution and incidence of complications on age at disease onset [8–14] have been reported.

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In a well-referenced study, Beaugerie *et al.* [15] reported clinical factors that were present at the time of CD diagnosis that were predictive of a disabling disease course over the subsequent 5 years, including age less than 40 years and perianal disease; disabling disease was defined as steroid dependency, hospitalization, and need for immunosuppression, resection, or perianal surgery. Other researchers have identified ileal or ileocolonic disease, upper GI or extensive small bowel involvement, stricturing behavior, and deep colonic ulcerations as risk factors for a disabling disease course [16–24]. In individuals with UC, a higher education, female sex, and smoking were found to be risk factors for flare-ups during the first 10 years [25]. It additionally has been reported that disease behavior during this period is more aggressive in paediatric onset compared to adult onset patients [26–28].

To date, no such data on patients with IBD are available in Switzerland. Therefore, in 2006, a nationwide cohort study on patients with IBD, the SIBDC study, was started [29], including a pediatric subcohort. The aim of the present study was to characterize disease activity 10 years after diagnosis, with the primary question, whether 10 years after diagnose, disease behavior of patients with pediatric onset would still differ from that of patients with adult onset. For this purpose, we intended to analyze the following variables: need for surgery, the prevalence of EIMs and complications, the clinical situation, and therapy requirements at 10 years of diagnosis. A further aim of the study was to correlate disease activity with disease location and behavior at diagnosis, for both pediatric-onset and adult-onset IBD separately.

Patients and methods

Database

As of January 2017, 3582 patients diagnosed with CD, UC, or IBD-U according to standard criteria [29] were registered in the SIBDCS database. The study protocol for this cohort study was approved by the central and local ethics committees in Switzerland in 2006. Patient recruitment since 2006 was conducted at six university centers in Switzerland (Geneva, Lausanne, Bern, Basel, Zurich, and St Gallen), as well as in select regional centers, with the University of Lausanne serving as the coordinating center and housing the database [30]. Retrospective data since diagnosis were obtained from patient charts, and prospective clinical data were collected during medical visits at inclusion and follow-up visits by the patient's gastroenterologist or a specialized study nurse who completed clinical report forms. The forms were then sent to the data center for validation and data entry.

Patients

From this registry, all patients with a disease duration of 10 years (108–132 months), inclusion to the registry at any time after diagnosis, but participating actively 10 years after diagnosis, were included in our study. The following data were obtained from this database: date of birth, sex, family history of IBD (first degree relatives), age at IBD diagnosis and at inclusion, type of IBD (CD, UC, or IBD-U), and initial disease location (recorded according to Montreal classification) [31]. Furthermore, data on the occurrence of strictures (duodenojejunal, ileal, ileocaecal valve, colon, rectum and anus, and anastomosis, as diagnosed by endoscopic, radiologic, or surgical means), abdominal penetrating disease (enteroenteral, enterovesical, enterocutaneous fistulas and perforation, and intra-abdominal abscesses, defined as extraintestinal collections of fluid, as diagnosed by radiologic or surgical means), perianal disease (high and low perianal, perineal, vaginal, and chronic or acute anal fissures, vaginal fistulas, and perianal abscesses, as diagnosed by clinical, radiologic or surgical examination) in CD, and progression or extension of disease in UC were retrieved. In addition, data on the occurrence of EIMs (arthralgia/arthritis, uveitis/episcleritis, pyoderma gangrenosum or erythema nodosum, aphthous oral ulcers, ankylosing spondylitis, and primary sclerosing cholangitis), intestinal and other complications [colorectal cancer, colonic dysplasia, intestinal lymphoma, osteopenia as measured by dual-energy X-ray absorptiometry measurements according to guidelines, anemia (not owing to drugs), deep venous thrombosis or pulmonary embolism, gallstone or nephrolithiasis, malabsorption syndrome, massive lower GI hemorrhage, perforation, or peritonitis], the necessity of treatments, such as tumor necrosis α inhibitors (anti-TNFα), independent of success, failure, or cessation of adverse effects, of immunomodulators, corticosteroids or mesalazine, and the necessity for abdominal resectional surgery [small bowel, ileocaecal, or any type of colonic resection (right, left, sigmoid resection, subtotal colectomy, or total proctocolectomy)], or surgery for abscess drainage, fistulectomy, seton placement, fibrin/glue instillation, and mucosal sliding flap were obtained. The outcome was defined as the cumulative change of disease behavior, the occurrence of EIM or complications, or the need for medical or surgical therapies. Data on BMI and weight came from measurements taken by the study nurse at the enrollment visit and at follow-up, using the wall stadiometer and weight scales available at the various study centers. Weight and BMI data of healthy controls (HC) (10 209 female and 8138 male patients; 17–90 years) were obtained from the Federal Office of Public Health survey of 2007 [32]. The patients were grouped according to the Paris classification [33] into categories based on age at diagnosis (<10, <17, <40, or >40 years of age). The outcome variables were dichotomized into present or absent.

Statistical analysis

The distribution of continuous data was assessed using normal-QQ-plots. Gaussian distributed data are presented as the mean ± SD and range, and non-Gaussian distributed data are presented as the median and interquartile range (IQR). Differences in the distribution of continuous data between two or more groups were assessed using Student's *t*-test or analysis of variance for Gaussian data, and using the Wilcoxon–Mann–Whitney rank sum or independent-samples Kruskal–Wallis test for non-Gaussian data. Categorical data are presented as raw counts and relative percentages, and 95% confidence intervals were derived using Pearson–Klopper exact method. Differences in the distribution of categorical data between two or more groups were assessed using the χ^2-test or Fisher's exact test in cases of insufficient sample size. Bonferroni's correction was used for multiple testing. Multivariate linear

regression analysis was used to assess associations between ages at diagnosis, adjusted for sex, smoking, and initial disease location and continuous outcome variables. Multivariate logistic regression was used for dichotomous outcome variables. For the purpose of the present study, a *P*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS statistics 23.0 (IBM Corp., Armonk, New York, USA).

Results

After the exclusion of 26 patients with IBD-U, data of 481 patients with CD (235 male and 246 female patients) and 386 patients with UC (202 male and 184 female patients), a disease duration of 10 years, and an available annual follow-up during the time window of 108–132 months after the diagnosis could be obtained for analysis.

Patients with Crohn's disease

Initial disease location at diagnosis only differed between pubertal and older than 40 years patients. No comparison was possible for upper GI disease, because not enough patients had assessment of the upper GI at diagnosis (Table 1). Sex distribution concerning smokers and initial location was even in all age groups. At diagnosis, none of the <10-year-old, 11.1% of the <17-year-old, 52.8% of the <40-year-old, and 44.6% of the >40-year-old patients were smokers (<10 vs. <40 years: $P=0.003$, <10 vs. >40 years: $P=0.01$, and >17 years vs. > or <40 years: $P<0.001$). Ten years later, 12.5% of the <10-year-old, 23.8% of the <17-year-old, 38.4% of the <40-year-old, and 31.5% of the >40-year-old patients had started or continued smoking (<10 vs. > or <40 years: $P=$NS, <17 vs. <40 years: $P=0.03$, <17 vs. >40 years: $P=$NS) and 27.3% of the <40-year-old and 29.4% of the >40-year-old smokers had stopped smoking.

Disease behavior at 10 years after diagnosis was similar in all age groups, and the same was true for the occurrence of intestinal complications such as stenosis and abdominal or perianal fistulae or abscesses (Table 1). A snapshot of Crohn's disease activity index and C-reactive protein (CRP) values at 10 years after diagnosis yielded similar results. In addition, the rate of medical therapies administered during the 10 years of disease course was similar in all age groups, as was a snapshot of the rate of ongoing therapies at 10 years after diagnosis (Table 2).

Intestinal resectional surgery was less frequently performed, and anti-TNFα therapy was used more frequently in pediatric-onset patients, especially in those requiring intestinal resectional surgery (Table 2).

Aphthous stomatitis and ankylosing spondylitis were more frequently seen in those with disease onset at less than 10 years of age, but the difference was not significant, whereas arthralgia and osteopenia were more frequent in adult-onset CD (Table 3). Because of the small patient numbers in the pediatric age groups, none of the comparisons yielded significant results. Furthermore, vascular events, malabsorption syndrome, perforation, peritonitis, or intestinal neoplasia were rare complications and excluded from the analysis (Table 3). Patients with anti-TNFα therapy and disease onset at less than 40 years, the only really large patient group, had significantly higher rates of arthralgia (41/73 without TNFα and 108/96 with TNFα, $P=0.01$), uveitis (6/108 without and 26/178 with TNFα, $P=0.03$), apthous stomatitis (9/36 and 36/168, $P=0.02$), and ankylosing spondylitis (3/11 and 20/184, $P=0.02$). Only for anemia, in patients with disease onset at less than 17 years, the requirement of TNFα, as a marker for more severe disease yielded a difference (0/16 without TNFα vs. 14/33 with TNFα, $P=0.01$). When taking surgery as a marker of

Table 1. Patient's characteristics at diagnosis and after 10 years of disease evolution in Crohn's disease

	Age group at diagnosis				
	<10 years ($n=8$)[a]	<17 years ($n=63$)[b]	<40 years ($n=318$)[c]	>40 years ($n=92$)[d]	*P*-value
Age at last follow-up [median (IQR)] (years)	17.0 (2)	24.0 (11)	34.0 (10)	60.0 (12)	<0.001
Sex (male/female)	5/3	34/29	146/172	50/42	0.3
Initial disease location [*n* (%)]					
Ileal	1 (12.5)	9 (14.3)	71 (22.3)	23 (25.0)	<0.001
Colonic	1 (12.5)	10 (15.9)	69 (21.7)	33 (35.9)	0.046[a,c]*
Ileocolonic	4 (50.0)	38 (60.3)	156 (49.1)	31 (33.7)	0.006[a,d]*
Upper gastrointestinal only	1 (12.5)	0	3 (0.9)	0	0.003[b,d]*
NA	1 (12.5)	6 (9.5)	19 (6.0)	5 (5.4)	
Additional upper gastrointestinal	0	6 (9.5)	12 (3.7)	2 (3.8)	
Intestinal complications after 10 years [*n* (%, 95% CI)]					
Stenosis	2 (25, 3–65)	25 (40, 28–53)	123 (39, 33–44)	39 (42, 32–53)	0.8
Abscess	1 (13, 0–53)	18 (29, 18–41)	75 (24, 19–29)	18 (20, 12–29)	0.5
Abdominal fistula	2 (25, 3–65)	10 (16, 8–27)	46 (15, 11–19)	13 (14, 8–23)	0.9
Perianal fistula	0 (0, 0–37)	11 (18, 9–29)	65 (20, 16–25)	17 (19, 11–28)	0.5
Disease behavior after 10 years [*n* (%)]					
B1	5 (62.5)	32 (50.8)	178 (56.0)	49 (53.3)	0.9
B2	1 (12.5)	21 (33.3)	94 (29.6)	30 (32.6)	
B3	2 (25.0)	10 (15.9)	46 (14.5)	13 (14.1)	
B1p (%B1)	1 (20.5)	11 (34.4)	50 (28.1)	13 (26.5)	0.8
B2p (%B2)	0	11 (52.4)	33 (35.1)	5 (20.0)	0.051
B3p (%B3)	1 (50.0)	5 (50.0)	19 (41.3)	5 (38.5)	0.9
CDAI at 10 years [median (IQR)] (years)	6.0 (10)	20.0 (44)	31.0 (64)	26.0 (51)	0.07
CRP at 10 years [median (IQR)] (mg/l)	3.0 (6)	3.9 (10)	4.8 (6)	3.7 (7)	0.9

Disease behavior: B1 = inflammatory, B2 = stenosing, B3 = penetrating.
CDAI, Crohn's disease activity index; CI, confidence interval; CRP, C-reactive protein; IQR, interquartile range; p, perianal.
*Bonferroni corrected.

Table 2. Cumulative surgical and medical therapies in Crohn's disease

	Age group at diagnosis				
	< 10 years ($n = 8$)[a]	< 17 years ($n = 63$)[b]	< 40 years ($n = 318$)[c]	> 40 years ($n = 92$)[d]	*P*-value
Surgical therapies ever used [*n* (%, 95% CI)]					
Intestinal resectional surgery (including ostomy, anastomosis, or plasty)	3 (38, 9–76)	13 (21, 11–33)	105 (33, 28–38)	38 (41, 31–52)	0.04[b,d]
Surgery for abdominal or perianal fistula or abscesses	1 (13, 0–53)	17 (27, 17–40)	73 (23, 18–28)	20 (22, 14–32)	0.8
Any surgery	3 (38, 9–76)	25 (40, 28–53)	146 (46, 40–52)	45 (49, 38–60)	0.7
Medical therapies ever used [*n* (%, 95% CI)]					
5-ASA	7 (88, 47–100)	35 (56, 42–68)	193 (61, 55–66)	51 (55, 45–66)	0.3
Systemic CS	8 (100, 63–100)	55 (87, 77–94)	282 (89, 85–92)	76 (83, 73–90)	0.3
Immunomodulators	7 (88, 47–100)	60 (95, 87–99)	284 (89, 85–93)	80 (87, 78–93)	0.4
Calcineurin inhibitors	0 (0, 0–37)	0 (0, 0–6)	9 (2.8, 1–5)	0 (0, 0–4)	0.3
TNFα inhibitors	7 (88, 47–100)	47 (75, 62–85)	204 (64, 59–69)	50 (54, 44–65)	0.06[b,c,*]
TNFα inhibitors and intestinal surgery	3 (100)	12 (92.3)	69 (65.7)	21 (55.3)	0.1[b,d,*]
TNFα inhibitors, no intestinal surgery	4/7 (57.1)	35/47 (74.5)	135/204 (66.2)	29/50 (58.0)	0.3
Medical therapies, snapspot at 10 years of follow-up [*n* (%, 95% CI)]					
5-ASA	5 (63, 24–91)	16 (25, 15–38)	82 (26, 21–31)	20 (22, 14–32)	0.2[a,b,*], 0.1[a,c,*]
Systemic CS	6 (75, 35–97)	33 (52, 39–65)	153 (48, 43–54)	33 (36, 26–47)	0.2[a,d,*], 0.2[b,d,*]
Immunomodulators	4 (50, 16–84)	45 (71, 59–82)	190 (60, 54–65)	58 (63, 52–73)	0.3
Calcineurin inhibitors	0 (0, 0–37)	0 (0, 0–6)	3 (0.9, 0–3)	0 (0, 0–4)	1.0
TNFα inhibitors	6 (75, 35–97)	37 (59, 46–71)	179 (56, 51–62)	41 (45, 34–55)	0.1

Immunomodulators = azathioprine, purinethol, methotrexate; calcineurin inhibitors = cyclosporine, tacrolimus.
5-ASA, 5-aminosalicylic acid; CI, confidence interval; CS, corticosteroids; TNFα, tumor necrosis factor α.
*Bonferroni corrected.

Table 3. Cumulative extraintestinal manifestations and complications in Crohn's disease

	Age group at diagnosis				
	< 10 years ($n = 8$)[a]	< 17 years ($n = 63$)[b]	< 40 years ($n = 318$)[c]	> 40 years ($n = 92$)[d]	*P*-value
Extraintestinal manifestations [*n* (%, 95% CI)]					
Arthralgia	2 (25, 3–65)	19 (30, 19–43)	149 (47, 41–53)	51 (55, 45–66)	0.01
Uveitis	1 (13, 0–53)	5 (8, 3–18)	32 (10, 7–14)	10 (11, 5–19)	0.9
Pyoderma gangrenosum	0 (0, 0–37)	0 (0, 0–6)	4 (1, 0–3)	3 (3, 1–9)	0.4
Erythema nodosum	0 (0, 0–37)	6 (10, 4–20)	32 (10, 7–14)	3 (3, 1–9)	0.2
Aphtous oral ulcers	3 (38, 9–76)	9 (14, 7–25)	45 (14, 11–18)	9 (10, 5–18)	0.2
Ankylosing spondylitis	2 (25, 3–65)	1 (2, 0–9)	23 (7, 5–11)	9 (10, 5–18)	0.1[a,b,*]
Any extraintestinal manifestation	7 (88, 47–100)	30 (48, 35–61)	174 (55, 49–60)	55 (60, 49–70)	0.1
Complications [*n* (%, 95% CI)]					
Osteopenia	0 (0, 0–37)	13 (21, 11–33)	50 (16, 12–20)	36 (39, 29–50)	< 0.001
Anemia (any, except owing to drug-related adverse events)	3 (38, 9–76)	14 (22, 13–34)	68 (21, 17–26)	21 (23, 15–33)	0.7
Thromboembolic events	0 (0, 0–37)	1 (2, 0–9)	7 (2, 1–4)	5 (5, 2–12)	0.7
Gallstone	0 (0, 0–37)	0 (0, 0–6)	11 (4, 2–6)	5 (5, 2–12)	0.3
Nephrolithiasis	0 (0, 0–37)	0 (0, 0–6)	4 (1, 0–3)	5 (5, 2–12)	0.1[c,d,*]
Massive hemorrhage	0 (0, 0–37)	4 (6, 2–15)	14 (4, 2–7)	6 (7, 2–14)	0.7
Any complication	3 (38, 9–76)	27 (43, 30–56)	131 (41, 36–47)	50 (44, 44–65)	0.2

CI, confidence interval.
*Bonferroni corrected.

disease severity, no difference was found for the occurrence of EIMs or complications.

After adjusting BMI (kg/m^2) to that of the Swiss population of the same age, the differences between age groups corresponded to that observed in the normal population (data not shown). Ten years after disease onset, the median BMI *Z*-scores did not differ from that of healthy coevals in the youngest-onset female group [median *Z*-BMI patients – 0.73 vs. HC – 0.1 (IQR = 1.1), $P = 0.3$] but was lower in male patients [median *Z*-BMI patients – 0.88 vs. HC – 0.11 (IQR = 1), $P = 0.01$]. In those with pubertal disease onset, both male and female patients had a lower BMI *Z*-score [female patients – 0.5 (IQR = 1) vs. HC – 0.17 (IQR = 1), $P = 0.004$, male patients – 0.15 (IQR = 1) vs. HC – 0.09 (IQR = 1), $P = 0.02$]. Only female patients who were older than 17 years at onset and younger than 40 years after 10 years from diagnosis [female patients, median *Z*-BMI – 0.49 (IQR = 1) vs. HC – 0.17 (IQR = 1), $P < 0.001$; male patients – 0.1 (IQR = 1) vs. HC – 0.09 (IQR = 1), $P = 0.9$] and male patients who were older than 17 years at diagnosis and older than 40 years at 10 years from diagnosis [male patients – 0.27 (IQR = 0.9) vs. – 0.11 (IQR = 1), $P < 0.001$; female patients – 0.28 (IQR = 0.8) vs. HC – 0.16 (IQR = 1), $P = 0.5$] had lower *Z*-BMI than HC. In patients diagnosed after the age of 40 years, *Z*-BMI did not differ or was higher [female patients – 0.07 (IQR = 1) vs. HC – 0.16 (IQR = 1), $P = 0.2$, male patients = 0.44 (IQR = 1) vs. – 0.05 (IQR = 1), $P < 0.001$] compared with that of HC.

The rate of ileocolonic disease location was correlated with young age at diagnosis ($R = 0.11$, $P = 0.01$), but not anymore after 10 years. The rate of arthralgia ($R = 0.14$, $P = 0.001$) and the rate of nephrolithiasis ($R = 0.12$, $P = 0.007$) were positively correlated, and the rate of

growth impairment ($R = -0.195$, $P < 0.001$) was negatively correlated with increasing age at diagnosis. The younger the patient at diagnosis, the higher was the rate of perianal disease ($R = 0.92$, $P = 0.04$), the lower was the rate of resectional surgery ($R = 0.1$, $P = 0.14$), and the higher that of cumulative therapy with anti-TNFα antibodies ($R = 0.13$, $P = 0.004$).

The multivariate analysis showed that age at diagnosis, corrected for sex, initial disease location, and smoking, was associated with arthritis at any time, but not with any other outcome variable (Table 4).

Ulcerative colitis patients

The rate of pancolonic disease location was significantly higher in patients with disease onset at less than 10 years of age at diagnosis, and at 10 years after diagnosis, it was high in both age groups, the <10 and the <17 years old (Table 5). Sex distribution concerning smokers and initial location was even in all age groups. At diagnosis, none of the <10-year-old, 4% of the <17-year-old, 23.7% of the <40-year-old, and 17.8% of the >40-year-old patients were smoking (<10 vs. <40 years: $P = 0.02$, <10 vs. >40 years: $P = 0.053$, <17 vs. <40 years: $P = 0.02$, <17 vs. >40 years: $P =$ NS). At 10 years after the diagnosis, none of the <10-year-old, 16.0% of the <17-year-old, 13.8% of the <40-year-old, and 11.1% of the >40-year-old patients had started or continued smoking (all comparisons, $P =$ NS) and 41.7% of the <40-year-old and 37.5% of the >40-year-old smokers had stopped smoking. At the last follow-up, a snapshot of CRP values showed no difference between age groups, but Modified Truelove Witts Activity Index was lowest in the early-onset patients.

Intestinal resectional surgery has been carried out at similar rates in all age groups. Except for immunomodulators, which were most frequently used in those diagnosed at younger than 10 years, all medical treatments were used with similar frequency in all age groups (Table 6). Ten years after diagnosis, overall EIMswere least frequent in those with disease onset at less than 10 years of age. Anemia occurred most frequently in pediatric-onset patients (Table 7). Other complications, such as osteopenia, intestinal neoplasia, or gallstones and kidney stones have not been reported in patients diagnosed before 10 years of age. Patients with surgical interventions with disease onset at less than 17 years of age and less than 40 years of age had significantly higher rates of osteopenia (<17 years: 0/20 without and 3/2, $P = 0.004$ with surgery,

Table 4. Association of age at diagnosis, initial disease location, sex, and smoking with outcome at 10 years in patients with Crohn's disease (multivariate analysis[a])

	EIM: stomatitis	EIM: arthritis	Intestinal surgery	TNFα ever
Age group (years)				
<10	2.74 (0.48–15.59); 0.3	0.76 (0.13–4.30); 0.76	1.11 (0.16–7.70); 0.92	0.57 (0.15–2.15); 0.41
<17	1 (ref)	1 (ref)	1 (ref)	1 (ref)
<40	0.89 (0.39–2.03); 0.78	2.04 (1.11–3.76); 0.02	1.00 (0.27–3.74); 0.99	0.88 (0.37–2.08); 0.77
>40	0.61 (0.22–1.71); 0.34	2.99 (1.47–6.08); 0.00	0.98 (0.24–4.07); 0.98	0.86 (0.34–2.17); 0.74
Female sex	1.37 (0.79–2.36); 0.26	1.50 (1.03–2.17); 0.04	0.47 (0.22–1.00); 0.05	0.86 (0.56–1.36); 0.55
Initial location				
Not available	1.87 (0.57–6.14); 0.30	1.18 (0.51–2.73); 0.70	1.04 (0.32–3.37); 0.95	0.81 (0.37–1.75); 0.59
Ileal	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Clonic	1.83 (0.79–4.20); 0.16	1.22 (0.71–2.11); 0.47	0.84 (0.37–1.86); 0.66	0.97 (0.59–1.59); 0.90
Ileocolic	1.37 (0.64–2.94); 0.42	1.10 (0.68–1.77); 0.71	0.33 (0.07–1.49); 0.15	0.46 (0.22–0.96); 0.04
Upper gastrointestinal only	NA	1.69 (0.21–13.48); 0.62	–	–
Smoker at last visit	0.96 (0.49–1.90); 0.92	1.39 (0.57–2.23); 0.17	1.81 (0.59–5.56); 0.28	1.27 (0.63–2.56); 0.495
Smoker at diagnosis	1.14 (0.58–2.27); 0.70	0.84 (0.52–1.34); 0.46	0.27 (0.07–1.02); 0.05	0.71 (0.39–1.31); 0.274

EIM, extraintestinal manifestation; TNFα, tumor necrosis factor α.
[a]Expressed as odds ratio and 95% confidence interval for binary, and as linear regression coefficient and 95% confidence interval for continuous variables.

Table 5. Patient characteristics at diagnosis and after 10 years of disease evolution of ulcerative colitis

	Age group at diagnosis				
	<10 years ($n = 18$)[a]	<17 years ($n = 25$)[b]	<40 years ($n = 253$)[c]	>40 years ($n = 90$)[d]	*P*-value
Age at last follow-up [median (IQR)] (years)	15.5 (4)	24.0 (3)	38.0 (11)	29.0 (12)	<0.001
Sex (male/female)	6/12	15/10	125/128	56/34	0.06
Initial disease location [*n* (%)]					
Pancolitis	13 (72.1)	14 (56.0)	91 (36.0)	34 (37.8)	<0.05
Left sided	3 (16.7)	5 (20.0)	97 (38.3)	36 (40.0)	
Proctitis	0	2 (8.0)	41 (16.2)	13 (14.4)	
NA	2 (11.1)	4 (16.0)	24 (9.5)	7 (7.8)	
Disease location after 10 years [*n* (%, 95% CI)]					
Pancolitis	14 (77.8)	14 (56.0)	98 (38.7)	27 (30.0)	0.001, 0.1[a,c,*], 0.03[a,d,*]
Left sided	2 (11.1)	4 (16.0)	104 (41.1)	45 (50.0)	
Proctitis	1 (5.6)	6 (24.0)	49 (19.4)	15 (16.7)	
NA	1 (5.6)	1 (4.0)	2 (0.9)	3 (3.3)	
MTWAI at 10 years [median (IQR)]	0.0 (0)	2.0 (0)	2.0 (3)	2.0 (4)	<0.001
CRP at 10 years [median (IQR)] (mg/l)	4.0 (4)	3.5 (2.5)	2.8 (4)	3.0 (4)	0.2

Disease location: 1 = pancolitis, 2 = left sided, 3 = proctitis.
CI, confidence interval; CRP, C-reactive protein; IQR, interquartile range; MTWAI, Modified Truelove Witts Activity Index.
*Bonferroni corrected.

Table 6. Cumulative surgical and medical therapies in ulcerative colitis

	Age group at diagnosis				
	< 10 years ($n = 18$)[a]	< 17 years ($n = 25$)[b]	< 40 years ($n = 253$)[c]	> 40 years ($n = 90$)[d]	*P*-value
Resectional surgery [*n* (%, 95% CI)]	2 (11, 1–35)	3 (12, 3–31)	22 (9, 6–13)	9 (10, 5–18)	0.9
Medical therapies ever used [*n* (%, 95% CI)]					
5-ASA	16 (89, 65–99)	24 (96, 80–100)	241 (95, 92–98)	88 (98, 92–100)	0.4
Systemic CS	17 (94, 73–100)	21 (84, 64–95)	214 (85, 80–89)	76 (84, 75–91)	0.7
Immunomodulators	17 (94, 73–100)	20 (80, 59–93)	172 (68, 62–74)	65 (72, 62–81)	0.1[a,c,*], 0.2[a,d,*]
Calcineurin inhibitors	2 (11, 1–35)	4 (16, 5–36)	33 (13, 9–18)	8 (9, 4–17)	0.7
TNFα inhibitors	5 (28, 10–53)	10 (40, 21–61)	86 (34, 28–40)	31 (34, 25–45)	0.9
Medical therapies at 10 years [*n* (%, 95% CI)]					
5-ASA	14 (78, 52–94)	19 (76, 55–91)	188 (74, 68–80)	65 (72, 62–81)	0.9
Systemic CS	7 (39, 17–64)	11 (44, 24–65)	129 (51, 45–57)	35 (39, 29–50)	0.2
Imunomodulators	15 (83, 59–96)	18 (72, 51–88)	124 (49, 43–55)	42 (47, 36–57)	0.005, 0.2[a,c,*], 0.04[a,d,*]
Calcineurin inhibitors	0 (0, 0–19)	1 (5, 0–20)	17 (7, 4–11)	4 (4, 1–11)	0.6
TNFα inhibitors	3 (17, 4–41)	7 (28, 12–49)	64 (25, 20–31)	24 (27, 18–37)	0.8

Imunomodulators = azathioprine, purinethol, methotrexate; calcineurin inhibitors = cyclosporine, tacrolimus.
5-ASA, 5-aminosalicylic acid; CI, confidence interval; CS, corticosteroids; TNFα, tumor necrosis factor α.
*Bonferroni corrected.

Table 7. Cumulative extraintestinal manifestations and complications in ulcerative colitis

	Age group at diagnosis				
	< 10 years ($n = 18$)[a]	< 17 years ($n = 25$)[b]	< 40 years ($n = 253$)[c]	> 40 years ($n = 90$)[d]	*P*-value
Extraintestinal manifestations [*n* (%, 95% CI)]					
Arthralgia	1 (6, 0–27)	7 (28, 12–49)	77 (30, 25–37)	39 (43, 33–54)	0.009, 0.1[a,d,*]
Uveitis	0 (0, 0–19)	2 (8, 1–26)	16 (6, 4–10)	5 (6, 2–12)	0.7
Pyoderma gangrenosum	0 (0, 0–19)	1 (4, 0–20)	5 (2, 1–5)	1 (1, 0–6)	0.7
Erythema nodosum	0 (0, 0–19)	1 (4, 0–20)	10 (4, 2–7)	0 (0, 0–4)	0.2
Aphtous oral ulcers	2 (11, 1–35)	1 (4, 0–20)	16 (6, 4–10)	3 (3, 1–9)	0.5
Ankylosing spondylitis	0 (0, 0–19)	1 (4, 0–20)	11 (4, 2–8)	4 (4, 1–11)	0.8
PSC	0 (0, 0–19)	3 (12, 3–31)	5 (2, 1–5)	1 (1, 0–6)	0.02[b,c,*], 0.06[b,d,*]
Any type of extraintestinal manifestation	3 (17, 4–41)	12 (48, 28–69)	96 (38, 32–44)	42 (47, 36–57)	0.2[a,b,*], 0.1[a,d,*]
Complications [*n* (%, 95% CI)]					
Osteopenia	0 (0, 0–19)	5 (20, 7–41)	45 (18, 13–23)	19 (21, 13–31)	< 0.001
Anemia (any, except owing to drug-related adverse events)	10 (56, 31–78)	13 (52, 31–72)	59 (23, 18–29)	15 (17, 10–26)	< 0.001, 0.1[a,c; a,d,*], <0.001[b,c; b,d,*]
Thromboembolic events	0 (0, 0–19)	0 (0, 0–14)	10 (4, 2–6)	10 (11, 5–18)	0.06[c,d,*]
Gallstone	0 (0, 0–19)	0 (0, 0–14)	1 (0.4, 0–2)	7 (8, 3–15)	< 0.001
Nephrolithiasis	0 (0, 0–19)	0 (0, 0–14)	5 (2, 1–5)	4 (4, 1–11)	0.4
Massive hemorrhage	0 (0, 0–19)	3 (12, 3–31)	4 (2, 0–4)	1 (1, 0–6)	0.01[b,c,*], 0.06[b,d,*]
Growth failure	8 (44, 9–58)	2 (8, −3–19)	0 (0, 0–1)	0 (0, 0–4)	0.048[a,b; b,d,*], <0.001[a,c; a,d; b,c,*]
Any complication	11 (61, 36–83)	12 (52, 28–69)	97 (38, 32–45)	41 (46, 35–56)	0.2

CI, confidence interval; PSC, primary sclerosing cholangitis.
*Bonferroni corrected.

<40 years: 16/192 vs. 8/37, $P = 0.048$). Patients with anti-TNFα therapy and disease onset at less than 40 years of age, the only really large patient group, had significantly higher rates of arthralgia (50/126 without TNFα and 36/41 with TNFα, $P = 0.01$), osteopenia (61/147 without and 25/20 with TNFα, $P = 0.002$), or anemia stomatitis (50/144 and 36/23, $P < 0.001$).

After adjustment with the Swiss population of the same age, the differences in BMI between age groups corresponded to the differences in the normal population (data not shown). However, only patients diagnosed before the age of 10 years had BMI *Z*-scores comparable to their healthy age peers [female patients < 10 years, median *Z*-BMI: 0.15 (IQR = 1) vs. HC − 0.1 (IQR = 1.1), $P = 0.8$; male patients < 10 years, − 0.43 (IQR = 2) vs. HC − 0.11 (IQR = 1), $P = 0.4$]. In patients with disease onset at less than 17 years of age, female but not male patients had a lower mean *Z*-BMI than that of their healthy counterparts [female patients, median *Z*-BMI − 0.73 (IQR = 1) vs. HC − 0.17 (IQR = –), $P = 0.004$; male patients 0.41 (IQR = 4) vs. HC − 0.09 (IQR = 1), $P = 0.14$]. In patients diagnosed at > 17 and <40 years of age, both female and male patients had the same BMI as HC [female patients − 0.35 (IQR = 1) vs. − 0.17 (1), $P = 0.1$; male patients − 0.13 (IQR = 1) vs. HC − 0.09 (IQR = 1), $P = 0.4$] at 10 years after diagnosis, but in those > 17 years and > 40 years of age at diagnosis, female and male patients had a lower BMI *Z*-score than their healthy counterparts [female patients − 0.6 (IQR = 1) vs. − 0.16 (IQR = 1), $P = 0.002$, male patients 0.09 (IQR = 1) vs. HC − 0.11 (IQR = 1), $P = 0.02$] at 10 years after diagnosis. In patients older than 40 years of age at diagnosis, the median *Z*-BMI was lower in female patients [− 0.9 (IQR = 1) vs. HC − 0.16 (IQR = 1), $P < 0.001$] but not in male patients [− 0.01 (IQR = 2) vs. − 0.05 (IQR = 1), $P = 0.9$].

Pancolitis at diagnosis ($R = 0.11$, $P = 0.02$, Kendall's τb) and after 10 years ($R = 0.11$, $P = 0.02$) was correlated with younger age at diagnosis. The rate of arthralgia ($R = 0.15$,

Table 8. Association of age at diagnosis, initial disease location, sex, and smoking with outcome at 10 years in patients with ulcerative colitis (multivariate analysis[a])

	Arthralgia	Anemia	Immunomodulators ever	MTWAI at last follow-up	CRP at last follow-up
Age group (years)					
<10	0.14 (0.01–1.24); 0.08	0.72 (0.20–2.60); 0.62	3.52 (0.37–33.79); 0.28	−2.28 (−4.05 to −0.51); 0.01	8.33 (0.10–16.57); 0.05
<17	1 (ref)	1 (ref)	1 (ref)	0 (ref)	0 (ref)
<40	1.03 (0.40–2.62); 0.95	0.26 (0.11–0.63); 0.003	0.68 (0.24–1.94); 0.47	0.08 (−1.11–1.27); 0.90	−1.48 (−7.40–4.44); 0.62
>40	1.91 (0.71–5.13); 0.20	0.19 (0.07–0.51); 0.01	0.80 (0.26–2.46); 0.70	0.29 (−0.99–1.57); 0.66	0.01 (−6.47–6.49); 0.99
Female sex	1.54 (0.98–2.42); 0.06	2.81 (1.67–4.71); <0.001	0.97 (0.61–1.56); 0.91	−0.11 (−0.69–0.48); 0.73	0.32 (−2.70–3.34); 0.84
Initial location					
Not available	0.81 (0.35–1.85); 0.61	0.89 (0.38–2.07); 0.79	1.28 (0.51–3.23); 0.60	−0.06 (−1.12–1.00); 0.92	2.58 (−2.44–7.61); 0.31
Pancolitis	1 (ref)	1 (ref)	1 (ref)	0 (ref)	0 (ref)
Left sided	1.17 (0.70–1.96); 0.54	0.76 (0.43–1.35); 0.34	0.78 (0.45–1.35); 0.37	−0.30 (−0.97–0.38); 0.39	1.73 (−1.78–5.24); 0.33
Proctitis	1.06 (0.54–2.08); 0.88	0.40 (0.17–0.95); 0.04	0.23 (0.12–0.45); <0.001	−0.39 (1.38–0.40); 0.28	0.99 (−3.72–5.70); 0.68
Smoker at last visit	1.13 (0.55–2.29); 0.74	0.54 (0.22–1.36); 0.19	0.82 (0.40–1.71); 0.60	1.12 (0.18–2.07); 0.02	1.52 (−3.02–6.06); 0.51
Smoker at diagnosis	1.00 (0.54–1.82); 0.99	0.88 (0.43–1.81); 0.73	0.71 (0.39–1.30); 0.26	0.17 (−0.63–0.96); 0.68	−2.44 (−6.45–1.57); 0.23

CRP, C-reactive protein; MTWAI, Modified Truelove Witts Activity Index.
[a]Expressed as odds ratio and 95% confidence interval for binary, and as linear regression coefficient and 95% confidence interval for continuous variables.

$P = 0.002$), the rate of thrombotic events ($R = 0.14$, $P = 0.004$), and the presence of gallstones ($R = 0.19$, $P < 0.001$) were positively correlated with increasing age at diagnosis, whereas anemia was negatively ($R = -0.19$, $P < 0.001$) correlated with increasing age at diagnosis. No correlation was found with age at diagnosis and the need for resectional intestinal surgery or any medical therapy.

The multivariate analysis showed that age at diagnosis, corrected for sex, initial disease location, and smoking, was only associated with Modified Truelove Witts Activity Index and CRP at the last follow-up, but not with any of the other outcome variables (Table 8).

Discussion

Few studies have compared the disease evolution of various age groups over a period of 10 years. Two of these studies, the report of the IBSEN registry and that of the European collaborative study, collected data since 1990 [19,20]. Our registry included patients since 2006 and thus describes the disease evolution of a different period.

Within the first 10 years of the disease course of our patients with CD, intestinal complications, such as stenosing, penetrating disease, or perianal disease, occurred at a similar cumulative rate in all age groups, and disease behavior at 10 years was similar in all age groups. Differences in initial disease locations, smoking habits at diagnosis, or during the 10 years, as shown in our study, and a higher prevalence in B2 and B3 disease behavior or perianal disease at adult disease onset, as shown by others [20,24,34–37], did not result in an age-of-onset dependent rate of intestinal complications after 10 years of disease. Parallelly, no age of onset dependent differences for the rate of TNFα-antibody treatments, despite the increased use in our patients with pediatric-onset CD in comparison to earlier studies [38], or for the rate of surgical interventions were found and our rates were comparable with rates reported by others [5,39].

A similar picture emerged in our patients with UC; disease location, with the same initial age-group dependent distribution as already described by many groups [6,40], had not changed after 10 years. Still, the rate of surgical interventions was similar in all age groups, though lower than in other recent reports [40], and except for immunomodulators, medical therapies were used at a similar rate in all age groups and similar to rates reported by others [40].

We also looked at BMI *Z*-scores after 10 years and found a possible age of onset-dependent difference in patients with CD but not in those with UC. We could, however, not compare and confirm these findings with results of other larger cohorts [41,42]. Lastly, the overall frequency of EIMs or extraintestinal complications was similar in all age groups of patients with CD and those with UC, and to those of earlier reports [40,43–46].

We, however, found single age-dependent differences in the frequency of EIMs or complications. In both disorders, CD and UC, the rate of arthralgia and osteopenia was lower and that of anemia higher in pediatric-onset patients. Yet, the three disorders also affect the general population in an age-dependent manner. For example: peripheral joint pain and swelling have been reported in 14% of the general Italian adult [47], but not in the general pediatric population. Regarding bone loss, this is a process known to be associated with aging [48]. Moreover, bone mineral density is not routinely assessed in children and in patients with pediatric-onset IBD. Regarding the prevalence of anemia, especially iron-deficiency anemia is known to be more frequent in the general pediatric population [49,50]. Lastly, regarding gallstone disease, nephrolithiasis, and thromboembolic events, which are disorders with a higher prevalence in IBD than in the background population, their increasing incidence with older age in several countries has repeatedly been reported, and the prevalence in our cohort did not exceed that of the background population [51–53]. Therefore, the age-dependent rates of arthralgia, osteopenia, anemia, lithiases, and thromboembolic disease may at least partly reflect more a general than a disease-specific phenomenon.

Only the tendency toward an age-dependent distribution of aphthous stomatitis, with a high prevalence not only in our youngest-onset patients but also in other pediatric IBD cohorts [54], can be interpreted as disease specific. Effectively, the prevalence of aphthous stomatitis in the general population is similar in all age classes [55]. However, this result requires confirmation by analyses of larger cohorts.

Our findings are in contradiction with those of earlier reports. For instance, intestinal resectional interventions have been reported to be less frequently done in pediatric-onset patients, although, if done, these are carried out earlier during the disease course [56–58]. It must, however, be emphasized that the analyses of these latter studies have been done in patients with various disease durations. Our study is the first to compare rates of disease manifestations in patients with IBD of different age groups after a fixed period of time, and this cumulative view zooms off many of the differences.

The present study has several limitations: First, this study is not population based. In Switzerland, many adult patients with IBD are followed by gastroenterologists in private practice, particularly patients with uncomplicated diseases living in regions without easy access to university hospitals. Second, inclusion of patients to our registry occurred at different times after diagnosis, with variable durations of prospective follow-ups. Therefore, the chronology of the events, and their temporal relation could not be analyzed. Third, our pediatric groups were of small size and required the use of nonparametric tests leading to lower statistical power. Pooling of pediatric data from more registries would offer better insight into the chronology of disease-related events.

In summary, up to 10 years of follow-up, the course of the intestinal disease was not dependent on the age of onset of CD or UC. EIMs and complications seem to be age dependent. Arthralgia and osteopenia occur more often in adult-onset patients, whereas anemia and aphthous stomatitis are more frequent in the pediatric-onset patient.

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Conflicts of interest

There are no conflicts of interest.

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